II. Non-Technical Abstract

Anti-CEA Immunoglobulin-T Cell Receptor (αCEA-IgTCR)-Modified T Cells in Cancer Therapy

T cells can penetrate into virtually any area of the body and are the immune cells responsible for carrying out the actual elimination of pathogens. The ability of T cells to do this is controlled by activation signals transmitted through the T cell receptor (TCR). This normally involves a complex system of helper cells and other signal proteins that regulate and control T cell killing. The primary purpose of this signaling system is to guide the immune system in determining whether or not to mount an immune response.

T cells are capable of killing tumor cells but are usually blocked from doing so because they cannot discriminate between normal cells and cancerous cells. The goal of this proposal is to test a technique in which we remove immune cells from cancer patients, genetically re-program them to recognize and attack cancer cells, and then reinfuse them into the patient. This is accomplished by inserting a chimeric gene into the T cells. The product of this gene is a hybrid protein that directs the T cell to recognize and bind to the cancer cell. Once this binding occurs the same hybrid protein directly activates the T cell to kill the tumor cell it is bound to. An important aspect of this type of immune modification is that it bypasses or "short circuits" the normal controls that regulate T cell immunity. This "short circuiting" is essentially what allows the T cells to aquire the ability to discriminate between cancerous cells and normal cells, and thereby to target the tumor for destruction. We have shown in the laboratory that the gene-modified T cells are able to discriminate between the target tumor cells and other non-target cells. Further, once they recognize and bind to the target tumor they activate their immune functions and rapidly kill the cancer cells.

The tumor types that we will initially target are colon and rectal carcinoma, breast cancer, pancreatic cancer and others. Although we will initially test this technology on only these tumor types, the general principles and techniques are applicable to many other types of cancer. In addition, the methods we will use involve new gene therapy technologies which would have broad applicability to many different human diseases.